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(54) Title: MODIFIED STARCH FILM COMPOSITIONS			
(57) Abstract <p>The invention concerns compositions from modified starches, such as starch ethers or oxidized starch, more particularly hydroxypropylated starch (HPS) or hydroxyethylated starch (HES) for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard capsules. The hard capsules obtained by the present invention with a conventional dipping molding process are similar to hard gelatine capsules (HGC).</p>			

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Modified Starch Film Compositions

The invention concerns compositions from modified starches, such as starch ethers and oxidized starch, more particularly
5 hydroxpropylated starch (HPS) and hydroxyethylated (HES) for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard capsules. The hard capsules obtained by the present
10 invention are similar to hard gelatine capsules (HGC).

A second embodiment of the invention is the use of the modified starch compositions for the manufacturing of hard capsules by conventional dip moulding process as normally
used in the production of conventional hard gelatine
15 capsules.

For the industrial manufacture of pharmaceutical capsules gelatine is most preferred for its gelling, film forming and surface active properties. The manufacture of hard gelatine capsules by dip moulding process exploits fully its gelling
20 and film forming abilities. Such capsules are manufactured by dipping mould pins into a hot solution of gelatine, removing the pins from the gelatine solution, allowing the gelatine solution attached on pins to set by cooling, drying and stripping the so-formed shells from the pins. The setting of
25 the solution on the mould pins after dipping is the critical step to obtain a uniform thickness of the capsule shell.

Attempts have been made to manufacture capsules with materials other than gelatine, notably with modified cellulose. Successful industrial examples are the capsules
5 made of hydroxypropyl methylcellulose (HPMC). The HPMC capsules show several advantages over HGC. However, the raw material HPMC is significantly more expensive than gelatine.

Starch is another abundant natural polysaccharide which is renewable, biodegradable and of low cost. Because of the
10 limited film forming ability and poor mechanical properties, the success in this field is more limited. A unique industrial example (US 4,738,724) are starch capsules produced by injection moulding, but such capsules have a much higher shell thickness and a different shape which requires
15 specific filling and closing equipment.

US 4,026,986 describes the manufacture of HPS capsules by dip moulding process. However, due to the absence of setting ability of HPS solution, the dipping time is long (20 seconds), and therefore it did not result in commercial
20 process.

Surprisingly, we found that the addition of a very small amount of a setting system, preferably consisting of hydrocolloids, most preferably polysaccharides, confers to HPS OR HES solution an appropriate setting ability with the
25 result that hard HPS OR HES capsules can be manufactured by the dip moulding process of hard gelatine capsules under conventional process conditions.

The aim of the invention is therefore the provision of compositions based on HPS or HES for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably
5 for containers for predosed formulations like soft or hard capsules and wherein the HPS or HES compositions have in aqueous solution a sufficient setting ability.

The first object of the invention is compositions based on HPS or HES to improve and adjust the mechanical properties of
10 films for various applications.

We found that the addition of a plasticizer in the formulation can improve dramatically the HPS OR HES film flexibility. The plasticizer or mixture of plasticizers is selected from polyethylene glycol, glycerol, sorbitol,
15 sucrose, corn syrup, fructose, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propylenglycol, mono-, di- or triacetates of glycerol, or natural gums. Preferred are glycerol, polyethylene glycol, propylene glycol, citrates and their combinations. The amount of plasticizer depends on
20 the final application. For hard film formulations, such as for hard capsules, the plasticizer is contained in an amount of 0 to 20%, preferably 10-20%. A higher content, 20-30%, is preferred for soft film formulations, such as for soft capsules.

25 We found also that it is possible to further improve the film mechanical properties, by combining the HPS or HES with other hydrosoluble polymers or polysaccharides. The preferable

examples are pectin, alginates, polyvinyl alcohol and high molecular weight polyethylene glycol.

The second object of the present invention is the achievement of an adequate setting ability of the HPS OR HES solution for
5 process purpose.

The addition of a setting system, preferably based on polysaccharides, to HPS OR HES solutions enables the adaptation of specific and desired gelling properties for a selected process (film forming or dip moulding such as the
10 production of hard HPS OR HES capsules by a conventional dipping process). For the production of hard capsules by dip moulding process, it is extremely important that the film forming HPS OR HES solution remaining on the mould pins after dipping is prohibited from flowing down the pins. Otherwise
15 the obtained film will not have the desired uniform thickness.

With the compositions of the present invention we can produce hard HPS OR HES capsules with the same equipment and in the same range of process conditions as used for the production
20 of conventional hard gelatine capsules. Furthermore capsules produced from compositions of the instant invention have the same dimensional specifications and allow the use of the existing filling machinery and do not require specific and new equipment for the filling process.

25 The HPS OR HES concentration in the dipping solution is in a range of 10 to 50%, preferably in the range of 20 to 40% by weight.

The setting system consists of a hydrocolloid or mixtures of hydrocolloids and may contain in addition cations and/or sequestering agents.

Suitable hydrocolloids or mixtures producing synergistic properties may be selected from natural seaweeds, natural seed gums, natural plant exudates, natural fruit extracts, biosynthetic gums, gelatines, biosynthetic processed starch or cellulosic materials, preferred are polysaccharides.

The preferred polysaccharides are alginates, agar gum, guar gum, locust bean gum (carob), carrageenan, tara gum, gum arabic, ghatti gum, Khaya grandifolia gum, tragacanth gum, karaya gum, pectin, arabian (araban), xanthan, gellan, starch, Konjac mannan, galactomannan, funoran, and other exocellular polysaccharides. Preferred are exocellular polysaccharides.

The preferred exocellular polysaccharides are xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan, and dextran.

The preferred hydrocolloids are kappa-carrageenan or gellan gum or combinations like xanthan with locust bean gum or xanthan with konjac mannan.

Among the setting systems mentioned above, the systems of kappa-carrageenan with cation and gellan gum with cation are specifically preferred. They produce high gel strength at low concentrations and have excellent compatibility with HPS.

The amount of the hydrocolloid is preferably in the range of 0.01 to 5% by weight and especially preferred 0.03 to 1.0% in the aqueous HPS OR HES solution.

The cations are preferably selected from K^+ , Na^+ , Li^+ , NH_4^+ , Ca^{++} or Mg^{++} , for kappa-carrageenan is preferred K^+ , NH_4^+ or Ca^{++} . The amount of cations is preferably less than 3%, especially 0.01 to 1% by weight in the aqueous HPS OR HES solution.

The preferred sequestering agents are ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, edetic acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta cyclodextrin and combinations thereof. Especially preferred is ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof. The amount is preferably less than 3%, especially 0.01 to 1% by weight of the dipping solution.

The inventive HPS OR HES compositions may contain in a further aspect additional pharmaceutically or food acceptable colouring agents in the range of from 0 to 10% based upon the weight of the film. The colouring agents may be selected from azo-, quinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes or mixtures thereof. Examples are patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron

oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.

The HPS OR HES capsules of the invention may be coated with a
5 suitable coating agent like cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid gelatines, hypromellose phthalate, hydroxypropylmethyl cellulose phthalate, hydroxyalkyl methyl cellulose phthalates or mixtures thereof to provide e.g. enteric properties.

10 The HPS OR HES capsules of the invention may be used for the production of containers for providing unit dosage forms for example for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, flavouring agents and the like.

The HPS OR HES capsules of the invention may be used where a
15 release of filled product must occur at low temperature, such as at room temperature, which is not achievable with gelatine capsules.

The following examples and tests demonstrate the HPS OR HES capsule production and properties:

20 **Example 1: Production of HPS capsules with 15% plasticizer**

1.5 kg of HPS powder is mixed with 25 g of kappa-carrageenan. To 3.21 kg of deionised water under stirring is added 0.5 g of potassium acetate (0.01% by weight in the solution) and 265 g of glycerol (5.3% in solution and 15% in capsule),
25 followed by addition of the above mixture (30% of HPS and 0.5% of carrageenan in the solution). After the HPS is well dispersed, the dispersion is heated up to 90°C under slow

stirring, then held under strong stirring for 10 minutes to assure a good solubilisation of the components.

The HPS solution thus prepared is defoamed under slow stirring and then poured into a dipping dish of a pilot machine of conventional hard gelatine capsule production equipment. While keeping the dipping HPS solution at 60°C, natural transparent hard HPS capsules of size 0 were produced according to the conventional process with the same dimensional specifications to the conventional hard gelatine capsules.

Disintegration test results (according to USP XXIII 1995-<701> Disintegration):

First leak time: 21 seconds

Total disintegration time: 263 seconds.

Example 2: Production of HPS capsules with 10% PVA and 10% plasticizer

1.4 kg of HPS powder is mixed with 10 g of kappa-carrageenan and 175 g of PVA (PVA has a viscosity of 33 cps at 4% and 20°C). To 3.21 kg of deionised water under stirring is added 5 g of potassium acetate (0.10% by weight in the solution) and 175 g of glycerol (3.5% in solution and 10% in capsule), followed by addition of the above mixture (28% of HPS, 0.20% of carrageenan and 3.5% of PVA in solution). After the HPS is well dispersed, the dispersion is heated upto 90°C under slow stirring, then held under strong stirring for 30 minutes to assure a good solubilisation of the components.

The HPS solution thus prepared is defoamed under slow stirring and then poured into a dipping dish of a pilot machine of conventional hard gelatine capsule production equipment. While keeping the dipping HPS solution at 60°C, 5 natural transparent hard capsules of size 0 were produced according to the conventional process with the same dimensional specifications to the conventional hard gelatine capsules.

Disintegration test results:

10 First leak time: 51 seconds

Total disintegration time: 225 seconds

Example 3: Production of HES capsules with 10% plasticizer

1.30 kg of HES powder is mixed with 4.00 g of gellan. To 3.55 kg of deionised water under stirring is added 5.00 g of 15 potassium acetate (0.10% by weight in the solution), 2.00 g of ethylenediaminetetraacetic acid disodium salt (0.04%) and 145 g of glycerol (2.90% in solution and 10% in capsule), followed by addition of the above mixture (26.0% of HES and 0.08% of gellan in solution). After the HES is well 20 dispersed, the dispersion is heated upto 98°C under slow stirring, then held under strong stirring for 10 minutes to assure a good solubilisation of the components.

The HES solution thus prepared is defoamed under slow stirring and then poured into a dipping dish of a pilot 25 machine of conventional hard gelatine capsule production equipment. While keeping the dipping HES solution at 60°C, natural transparent hard capsules of size 0 were produced

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according to the conventional process with the same dimensional specifications to the conventional hard gelatine capsules.

Disintegration test results:

5 First leak time: 28 seconds

Total disintegration time: 443 seconds

We claim:

1. Film forming compositions consisting of modified
starches, such as starch ethers or oxidized starch, more
particularly hydroxypropylated starch or hydroxyethylated
starch and a setting system.
5
2. Film forming compositions according to claim 1, wherein
the setting system consists of hydrocolloids and cations.
3. Film forming compositions according to claim 1, wherein
the setting system contains optionally sequestering
agents.
10
4. Film forming compositions according to claim 1, wherein
the content of hydroxypropylated starch is 88 to 98% by
weight, of water is 2 to 12% by weight, of
polysaccharides is 0.01 to 10%, preferably 0.05 to 5% by
weight and of cation is 0.001 to 5%, preferably 0.01 to
3% by weight.
15
5. Film forming compositions according to claim 1, wherein
the hydrocolloids of the setting system are selected from
polysaccharides.
- 20 6. Film forming compositions according to claim 1, wherein
the hydrocolloids of the setting system are selected from
alginates, agar gum, guar gum, locust bean gum (carob),
carrageenan, tara gum, gum arabic, ghatti gum, Khaya
grandifolia gum, tragacanth gum, karaya gum, pectin,
25 arabian (araban), xanthan, gellan, starch, Konjac mannan,
galactomannan, or funoran.

7. Film forming compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from exocellular polysaccharides.
8. Film forming compositions according to claim 1, wherein
5 the hydrocolloids of the setting system are selected from xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan, or dextran.
9. Film forming compositions according to claim 1, wherein
10 the hydrocolloids of the setting system are selected from gellan gum or kappa-carrageenan.
10. Film forming compositions according to claim 1, wherein the optional sequestering agent or mixture of
15 sequestering agents of the setting system is selected from ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, edetic acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta cyclodextrin.
- 20 11. Film forming compositions according to claim 10, wherein the sequestering agent or mixture of sequestering agents is selected from ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof.
12. Film forming compositions according to claim 1 containing
25 additionally plasticizers in a range from about 0 to 40 % based upon the weight of the composition.
13. Film forming compositions according to claim 12 wherein the plasticizer or mixture of plasticizers is selected
30 from polyethylene glycol, glycerol, sorbitol, sucrose, corn syrup, fructose, dioctyl-sodium sulfosuccinate,

triethyl citrate, tributyl citrate, 1,2-propylenglycol, mono-, di- or triacetates of glycerol, or natural gums.

14. Film forming compositions according to claim 1 containing additionally colouring agents in a range from about 0 to 10 % based upon the weight of the composition.
15. Film forming compositions according to claim 14 wherein the colouring agent or mixture of colouring agents is selected from azo-, quinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes.
16. Film forming compositions according to claim 15 wherein the colouring agent or mixture of colouring agents is selected from patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, or brilliant black BN.
17. Film forming compositions according to claim 14 wherein the colouring agent or mixture of colouring agents is selected from carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.
18. Containers for unit dosage forms for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, or flavouring agents produced from the compositions according to claims 1 to 17.
19. Container according to claim 18 which is a pharmaceutical capsule.

20. Containers according to claim 18, characterised in that the container has a coating.
21. Coated containers according to claim 20 wherein the coating is selected from cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid gelatines, hypromellose phthalate, hydroxypropylmethyl cellulose phthalate hydroxyalkyl methyl cellulose phthalates or mixtures thereof.
22. Caplets encapsulated in film forming compositions according to claim 1.
23. Capsules according to claim 18 characterised in that the capsule halves are sealed with one or more layers of the composition according to claims 1 to 17.
24. Capsules according to claim 18 characterised in that a liquid fusion process seals the capsule halves.
25. Capsules according to claim 18 characterised by a release of filled product at low temperature, such as at room temperature.
26. Aqueous solutions of compositions according to claims 1 to 17 for the manufacturing of capsules.
27. Aqueous solutions according to claim 26, containing hydroxypropylated starch or hydroxyethylated starch in an amount of 10 to 60 %, preferably 20 to 40 % by weight, hydrocolloids in an amount of 0.01 to 5 %, preferably 0.03 to 1.0 % by weight and cations in an amount of 0.001 to 3 %, preferably 0.01 to 1 % by weight of the aqueous solution.

28. Aqueous solutions according to claim 26, containing optionally sequestering agents in an amount of 0.001 to 5 %, preferably 0.01 to 3 % by weight of the aqueous solution.
- 5 29. Use of aqueous solutions according to claim 26 for the manufacturing of hard capsules in a dip moulding process.
30. Manufacturing of hard capsules from aqueous hydroxypropylated starch solutions according to claims 26 to 28 in a dip moulding process with conventional hard
10 gelatine capsules process parameters and equipment.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08L3/08 C08L3/18 C09D103/08 C08L3/10 C09D103/10
 A61K9/48 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C09D C08L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 378 546 A (TOSHIO TSUZUKI ET AL.) 16 April 1968 (1968-04-16) column 2, line 54 - line 57 ---	1
A	DATABASE WPI Week 199307 Derwent Publications Ltd., London, GB; AN 1993-055171 XP002122906 "Soft capsule agent having controlled adhesivity during packaging etc. - has blended food fibre e.g. agar, carrageenan etc. in capsule film" & JP 05 004914 A (ASAHI KASEI KOGYO KK ET AL.), 14 January 1993 (1993-01-14) abstract --- -/--	1,6-10, 19,20, 23,27,28

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 026 986 A (CHRISTEN ET AL.) 31 May 1977 (1977-05-31) cited in the application the whole document ---	1, 19, 27, 30, 31
A	US 5 224 989 A (LIKAROVA) 6 July 1993 (1993-07-06) abstract claims ---	1, 3, 11-19, 23, 27-29
A	EP 0 606 486 A (TEIJIN LIMITED) 20 July 1994 (1994-07-20) abstract -----	1, 2, 6, 7, 19, 23, 27

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Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3378546	A	16-04-1968	NONE	
JP 5004914	A	14-01-1993	NONE	
US 4026986	A	31-05-1977	NONE	
US 5224989	A	06-07-1993	NONE	
EP 606486	A	20-07-1994	AU 660824 B	06-07-1995
			AU 4355593 A	04-01-1994
			US 5626871 A	06-05-1997
			AU 659328 B	11-05-1995
			AU 4355693 A	04-01-1994
			CA 2115065 A	23-12-1993
			CA 2115444 A	23-12-1993
			EP 0611567 A	24-08-1994
			WO 9325193 A	23-12-1993
			WO 9325198 A	23-12-1993
			JP 2907551 B	21-06-1999